## Remarks

Applicants request reconsideration and timely notice of allowance. As explained below, the claims are in condition for allowance.

The Examiner noted the reference to amended claim 40. The language in claim 40 has not been amended since it was originally presented in the Preliminary Amendment of August 14, 1997. Any reference to an amendment to claim 40 was inadvertent.

**Rejection under 35 U.S.C. § 112, second paragraph.**

The Examiner asserts that claims 61-64 are incomplete as allegedly omitting essential steps. Applicants respectfully disagree.

The Examiner apparently considers the steps of "whether or not the gene of interest is expressed" and "whether the survival of the cells has been prolonged" as essential (*see* Paper No. 16 at page 2). Applicants' claims should be read in light of the specification and with the reasonable understanding of one skilled in the art. Taking these factors into account, applicants respectfully submit that one of skill in the art would need no further recitations in these claims in order to understand them.

First, the preamble of the claim indicates that the gene of interest is expressed in the cell ("A method of prolonging the survival of a cell expressing a gene of interest. . .", *see* claim 61). One of skill in the art understands that the cell expresses the gene of interest, whether or not a specific recitation of a separate step for "expressing" exists. If the cell expresses the gene of interest *in vivo* or *in vitro* does not matter and would not alter one's understanding of the subject matter.

Second, the preamble also indicates the "prolonging the survival" aspect of the claimed subject matter. One skilled in the art would understand this as a result of the inventive method and not necessarily a separate step in the method. Furthermore, the "detecting the presence of mRNA or protein expressed" (*see* claim 61) would inherently detect a state of the cell and its survival. The surviving cells will express mRNA or protein. No further explanation is required.

Applicants respectfully request reconsideration and withdrawal of this rejection.

**Rejection under 35 U.S.C. § 112, first paragraph.**

Claims 26-64 stand rejected under 35 U.S.C. § 112, first paragraph, as the specification allegedly does not reasonably provide enablement for the claims. Applicants respectfully disagree.

The Examiner states that certain aspects of the invention corresponding to the Examples are enabled, but that any composition comprising an immunosuppressive agent and a recombinant adenovirus has not been enabled. In particular, the Examiner notes the combination of anti-CD3 or anti-CD4 antibodies with gp19K-expressing adenovirus, noted in Examples 1 and 2. The Examiner apparently finds these aspects of the claims properly enabled. However, it is unclear why the Examiner considers other combinations of immunosuppressive agents and recombinant adenoviruses not enabled. There does not seem to be any discussion of inoperative combinations in the Office Action. Without some showing of why the applicants' presumptively enabled claims and presumptively enabling disclosure in the application cannot be made or used, the Patent Office has failed to present a *prima facie* case of lack of enablement.

Applicants incorporate by reference the comments submitted at pages 5-9 in the Response to Paper No. 13. There, applicants addressed both the statutory standard applicable

and the lack of any evidence contrary to applicants' assertions of enablement. The fact that applicants have not demonstrated by example every possible combination, or even some particular number of combinations, does not compel a conclusion of non-enablement. Some evidence of non-enabling species or some reason to doubt applicants' assertions must be presented. As there is no such evidence, a *prima facie* case of enablement has not been made. For these reasons, applicants respectfully request the withdrawal of this rejection.

Applicants have previously submitted evidence supporting the enablement of the claims (*see* Response to Paper No. 13 and the papers submitted and discussed). It is unclear if this evidence has been fully considered. Applicants request an Examiner's Interview to discuss this evidence and other issues relevant to the disposition of this application. Applicant's representative will contact the Examiner approximately one month after the filing of this paper to arrange a convenient date.

The Examiner also discusses the impact of the recitation "therapeutic gene" and the general considerations of "claims that read on gene therapy" (*see* pages 4-5 of Paper No. 16). The Examiner cites documents during this discussion. Applicants note that the claims are not limited to therapeutic applications for gene therapy in humans. It is unclear why the Patent Office has focussed on this one aspect of the claims. If other uses are enabled, which the Examiner does not seem to question, applicants submit that the claims have been properly enabled. There is no requirement that applicants exemplify every possible embodiment of their invention.

The documents noted in Paper No. 16 (Verma and Eck, of record) appear to relate to factors not particularly relevant to the issues the Patent Office reviews. Clinical success and effectiveness demonstrated through human clinical trials is a matter for the FDA to consider, not

the Patent Office. The assertion that "numerous factors complicate the gene therapy art" in relation to the FDA approval and review standards does not seem relevant here.

Applicants note the statements from the Federal Circuit's decision in *In re Brana*: the Patent Office must not confuse "the requirements under the law for obtaining a patent with the requirements for obtaining government approval to market a particular drug for human consumption." *In re Brana,* 34 U.S.P.Q.2d 1436, 1442 (Fed. Cir. 1995). Quoting the C.C.P.A. from *In re Krimmel*, the court in *Brana* explained further:

> We hold as we do because it is our firm conviction that one who has taught the public that a compound exhibits some desirable pharmaceutical property in a standard experimental animal has made a significant and useful contribution to the art, even though it may eventually appear that the compound is without value in the treatment of humans.
>
> *In re Brana,* 34 U.S.P.Q.2d 1436, 1442-3 (Fed. Cir. 1995).

Similarly, the methods and compositions claimed here should not be reviewed under a clinically effective standard of the FDA. Both the Verma and Eck documents clearly relate to clinical trial type evidence (*see* page 239, first paragraph of Verma, and Table 5-1 of Eck). Applying the correct standard here leads one of ordinary skill in the art to a conclusion that applicants have indeed enabled a useful invention. As discussed above, nothing in Paper No. 16 contradicts this conclusion.

Finally, the Patent Office notes the "surprising" and "unexpected" words used in a prior response of December 13, 1999 (*see* pages 5-8 of Paper No. 16). It appears that the Patent Office is using these words, written in the context of an obvious rejection that has since been withdrawn, to construct an argument that the use of certain genes and certain combinations is unpredictable. As noted previously and above, the Patent Office has provided no objective

evidence to support its assertions of non-enablement and no evidence that applicants' statements concerning enablement are incredible. In light of this, it seems particularly inappropriate to use the applicants' own evidence of nonobviousness to attempt to make a case of nonenablement.

Applicants have provided evidence that the combination of an expressed immunoprotective gene and an immunosuppressive agent creates effects on cells that can be used in a variety of aspects. One aspect is the prolonged ability to express a second gene (*see*, for example, Example 2.3). Nothing the Patent Office has cited and no arguments provided by the Patent Office detracts from this showing by the applicants. How the immunosuppressive agent and the immunoprotective gene can synergistically interact also does not detract from applicants' showing of prolonged expression. That others may not have predicted the prolonged expression, or any other advantage of the invention, also does not detract from applicants' showing.

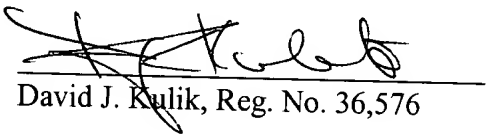
Applicants submit that the Patent Office's arguments that only the prolonged expression of ß-gal in the liver, or only some particularly exemplified combination of immunoprotective gene and immunosuppressive agent is enabled, lacks sufficient objective evidence of non-enablement. Without such evidence, a *prima facie* case of lack of enablement has not been made. Viewing all of applicants' arguments and evidence demonstrating enablement in comparison to the lack of evidence from the Patent Office, applicants respectfully request reconsideration and withdrawal of this rejection.

Applicants have provided for a two-month extension above. No additional extension of time fees, requests for extension of time, petitions, or additional claim fees are believed to be necessary to enter and consider this paper. If, however, any extensions of time are required or any fees are due in order to enter or consider this paper or enter or consider any paper

accompanying this paper, including fees for net addition of claims, applicants hereby request any extensions or petitions necessary and the Commissioner is hereby authorized to charge our Deposit Account # 50-1640 for any fees. If there is any variance between the fee submitted and any fee required, including the extension of time fee and fee for net addition of claims, the Commissioner is hereby authorized to charge or credit Deposit Account No. 50-1640.

Respectfully submitted,
**Brobeck, Phleger & Harrison LLP**

Date: May 29, 2001



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